The New York Times | http://nyti.ms/2bnFtD7

SCIENCE

From Fins Into Hands: Scientists Discover a Deep Evolutionary Link

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MATTER AUG. 17, 2016

To help his readers fathom evolution, Charles Darwin asked them to consider their own hands.

“What can be more curious,” he asked, “than that the hand of a man, formed for grasping, that of a mole for digging, the leg of the horse, the paddle of the porpoise, and the wing of the bat, should all be constructed on the same pattern, and should include similar bones, in the same relative positions?”

Darwin had a straightforward explanation: People, moles, horses, porpoises and bats all shared a common ancestor that grew limbs with digits. Its descendants evolved different kinds of limbs adapted for different tasks. But they never lost the anatomical similarities that revealed their kinship.

As a Victorian naturalist, Darwin was limited in the similarities he could find. The most sophisticated equipment he could use for the task was a crude microscope. Today, scientists are carrying on his work with new biological tools. They are uncovering deep similarities that have been overlooked until now.

On Wednesday, a team of researchers at the University of Chicago reported that our hands share a deep evolutionary connection not only to bat wings or horse hooves, but also to fish fins.

The unexpected discovery will help researchers understand how our own ancestors left the water, transforming fins into limbs that they could use to move around on land.

To the naked eye, there is not much similarity between a human hand and the fin of, say, a goldfish. A human hand is at the end of an arm. It has bones that develop from cartilage and contain blood vessels. This type of tissue is called endochondral bone.

A goldfish grows just a tiny cluster of endochondral bones at the base of its fin. The rest of the fin is taken up by thin rays, which are made of an entirely different tissue called dermal bone. Dermal bone does not start out as cartilage and does not contain blood vessels.

These differences have long puzzled scientists. The fossil record shows that we share a common aquatic ancestor with ray-finned fish that lived some 430 million years ago. Four-limbed creatures with spines — known as tetrapods — had evolved by 360 million years ago and went on to colonize dry land.

For over two decades, Neil H. Shubin, an evolutionary biologist, has investigated this transition in two radically different ways.

On the one hand, he has dug up fossils that date back to the transition from sea to land. His discoveries include a 370 million-year-old fish called Tiktaalik, which had limb-like fins. It developed endochondral bones corresponding to those in our arms, beginning at the shoulder with the humerus, then the radius, ulna and wrist bones. But it lacked fingers, and still had a short fringe of fin rays.

When he is not digging for fossils, Dr. Shubin runs a lab at the University of Chicago, where he and his colleagues compare how tetrapods — mice, for example — and fish develop as embryos.

Their embryos start out looking very similar, consisting of heads and tails and not much in between. Two pairs of buds then develop on their flanks. In fish, the buds grow into fins. In tetrapods, they become limbs.

In recent decades, researchers have uncovered some of the genes that govern this development. In 1996, a team of French researchers studying mice discovered genes that are essential for the development of their legs.

When the scientists shut down two genes, called Hoxa-13 and Hoxd-13, the mice developed normal long bones in their legs. But their wrist and ankle bones failed to appear, and they did not grow any digits.

This discovery suggested that Hoxa-13 and Hoxd-13 genes tell certain cells in the tetrapod limb bud that they will develop into hands and feet.

Dr. Shubin knew that fish have genes related to Hoxa-13 and Hoxd-13. He wondered what those genes were doing, if anything, in developing fins. An experiment on fish might give him and his colleagues a clue.

"But we didn't have the means to do it until technology caught up with our aspirations," Dr. Shubin said.

In the 1990s, no one yet knew how to shut down genes in fish embryos. But that has changed in recent years, thanks to a new gene-editing technology called Crispr. Scientists can use it to readily alter genes in virtually any species.

In 2013, a postdoctoral researcher in Dr. Shubin's lab, Tetsuya Nakamura, started using Crispr to manipulate fish embryos. He chose zebrafish to study, because their transparent embryos make it easy to track their development.

Dr. Nakamura inserted bits of DNA into the fish versions of the Hoxa-13 and Hoxd-13 genes. The inserted DNA garbled the sequence of the genes, so that the fish could not make proteins from them.

Zebrafish with defective copies of both Hox genes grew deformed fins, the scientists found. But to their surprise, the fish failed to make fin rays. In the fish, their experiment showed, the Hox genes were controlling cells that became dermal bone rather than the endochondral bone found in our own limbs.

Dr. Shubin got a similar surprise when he saw the results of a parallel experiment run by Andrew R. Gehrke, a graduate student. Mr. Gehrke engineered zebrafish so that he could follow individual cells during the development of embryos.

In Mr. Gehrke's altered fish, cells that switched on the Hox genes started to glow. They kept glowing throughout development, until they reached their final location in the fish's body.

Mr. Gehrke observed that a cluster of cells started making the Hox proteins early in the development of fish fins. When the fins were fully developed, Mr. Gehrke found that the fin rays were glowing. In a similar experiment on mice, the digits and wrist bones lit up.

"Here we're finding that the digits and the fin rays have some sort of equivalence at the level of the cells that make them," Dr. Shubin said. "Honestly, you could have knocked me over with a feather — it ran counter to everything that I was expecting after working on this problem for decades."

The new study was important because it revealed that the development of fins and limbs follows some of the same rules, said Matthew P. Harris, a geneticist at Harvard Medical School. In both cases, the Hox genes tell a clump of embryonic cells that they need to end up at the far end of an appendage. "The molecular address is the same," said Dr. Harris, who was not involved in the study.

In zebrafish, the cells that get that molecular address end up making dermal bone for fin rays. In tetrapods like us, the research indicates, the same cells produce endochondral bone in our hands and feet.

The new discovery could help make sense of the intermediate fish with limb-like fins that Dr. Shubin and his colleagues have unearthed. These animals still used the molecular addresses their ancestors used. But when their cells reached their addresses, some of them became endochondral bone instead of fin rays. It may have been a simple matter to shift from one kind of tissue to another.

"This is a dial that can be tuned," Dr. Shubin said.

A version of this article appears in print on August 18, 2016, on page A1 of the New York edition with the headline: Fins Into Hands: An Evolutionary Link Is Found.